

Age and Antihypertensive Drugs (Hydrochlorothiazide, Bendroflumethiazide, Nadolol and Captopril)

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Three double-blind Veterans Administration Cooperative Studies are reviewed to determine age-related changes in response to antihypertensive agents. In the first study 312 patients received hydrochlorothiazide titrated from 25 to 100 mg twice daily to lower diastolic blood pressure (BP) to <90 mm Hg. Of 121 patients aged 55 to 65 the decrease in BP averaged -21.8/-12.9 mm Hg, while in the 191 patients younger than 55 the reduction averaged -15.7/-11.5 mm Hg ($p < 0.001$; $p = 0.048$, respectively). Both systolic and diastolic BP reductions averaged significantly more in older whites; in older blacks it was systolic BP only. An additional 298 patients received titrated doses of propranolol alone. In this group there were no significant differences in BP response between younger patients and patients aged 55 to 65 except in the subgroup of white patients older than 60, in whom the systolic

reduction was significantly less than in the younger patients.

In a second study of bendroflumethiazide alone and with nadolol, systolic BP decreased more in older than in younger patients but there was no age-related reduction with nadolol alone. In the third trial captopril was first given alone and later with hydrochlorothiazide. There were no age-related differences with captopril alone, but after the addition of hydrochlorothiazide there was a trend toward a greater antihypertensive response in the patients aged 55 to 69. Thus, responsiveness of older patients varies with the type of antihypertensive drug. Age appears to increase the antihypertensive response to thiazide diuretics but not to β -adrenergic blocking drugs or to captopril.

(Am J Cardiol 1988;61:117-121)

Hypertension in the elderly has a different hemodynamic profile than in the young.¹ It characteristically has a higher systolic blood pressure (BP) in relation to the diastolic level. This is due mainly to increased stiffness of the large arteries secondary to arteriosclerosis. Also, cardiac output, heart rate, stroke volume, blood volume, renal blood flow and plasma renin activity are lower than in younger hypertensive patients.

The prevalence of hypertension increases with age. According to the National Health Survey 34% of the

population aged 55 to 65 years have a BP ≥ 160 systolic, ≥ 95 mm Hg diastolic, or both.² Further, the elderly constitute an increasing percentage of the total population. Therefore, hypertension in the elderly is a major public health problem. Because of the many changes that occur with aging including differences in hemodynamics, elderly patients may respond differently than younger patients to antihypertensive drugs.³ For these reasons there has been considerable interest recently in the epidemiology³⁻⁵ and treatment⁶⁻⁷ of hypertension in the elderly.

The Veterans Administration Cooperative Study Group has carried out controlled trials of a number of antihypertensive drugs. These trials have included patients of various ages permitting comparison under controlled conditions of age-related responses to a variety of antihypertensive drugs. Age 55 was chosen as the line dividing young from old because it permitted a larger sample in the older age group.

From the Cooperative Studies Program, Medical Research Service, Veterans Administration, Washington, D.C. Manuscript received June 4, 1987; revised manuscript received September 11, 1987, and accepted September 12.

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*See the Appendix for principal participants.

TABLE I Blood Pressure Changes After Hydrochlorothiazide or Propranolol by Age

Change in Blood Pressure (mm Hg)										
Age <55					Age 55 to 65					
	No.	Systolic Base	Systolic Change	Diastolic Base	Diastolic Change	No.	Systolic Base	Systolic Change	Diastolic Base	Diastolic Change
Hydrochlorothiazide										
Blacks	112	143	-17	101	-13	59	156	-26 [†]	101	-14
Whites	79	142	-14	102	-10	82	152	-18*	101	-12*
All	191	142	-16	101	-12	121	154	-22 [†]	101	-13*
Propranolol										
Blacks	113	141	-8	101	-9	57	148	-9	101	-10
Whites	78	146	-14	103	-12	50	151	-12	102	-13
All	191	143	-10	101	-11	107	150	-11	101	-11

Comparing blood pressure changes for age <55 vs ≥55.

* $p < 0.05$.† $p < 0.001$.

Hydrochlorothiazide Versus Propranolol

Hydrochlorothiazide: The first study presents age-related data from a trial comparing hydrochlorothiazide with propranolol given as monotherapy.⁸ The trial included nonhospitalized male veterans aged 21 to 65 years with untreated diastolic BP between 95 and 114 mm Hg. After a single-blind placebo period of 4 weeks, patients with placebo counts indicating compliance and with diastolic BP in the acceptable range, were randomized to receive either propranolol or hydrochlorothiazide given double-blind. This was followed by a 10-week dose-finding period. Doses were increased until the diastolic BP decreased to <90 mm Hg (goal BP) or the maximum dose was reached or side effects intervened.

There were significant age-related effects associated with hydrochlorothiazide. The drug was titrated from 25 mg twice daily (50 mg/day), increasing until the diastolic BP remained below 90 mm Hg on 2 successive visits or until the maximum dose of 100 mg twice daily (200 mg/day) had been given. There were 121 patients aged 55 to 65 and 191 patients younger than 55 years (Table I). In those aged 55 to 65 the average reduction of BP was -21.8/-12.9 mm Hg (systolic/diastolic). Both the systolic and the diastolic BP decreases were significantly greater than in patients younger than 55 years. In the latter group, the BP decreased by -15.7/-11.5 mm Hg ($p < 0.001$; $p = 0.048$).

With respect to age and race, the age-related reductions were greater in blacks only with regard to systolic BP, the systolic reduction averaging -26.2 mm Hg in those aged 55 to 65 years and -17.2 mm Hg in patients younger than 55 years ($p < 0.001$). In whites both the systolic and diastolic reductions were significantly greater in older patients. In the group of whites aged 55 to 65, the reductions averaged -17.5/-12.1 mm Hg while those younger than 55 years the reductions were -13.6/-9.9 mm Hg ($p = 0.052$; $p = 0.018$). The racial differences were especially prominent in both age groups with significantly greater decreases, especially in systolic BP in blacks compared with whites in both age groups.

With respect to the percent of patients achieving goal diastolic BP <90 mm Hg with hydrochlorothiazide there also was a significant difference related to age (Table II). Among the patients aged 55 to 65, 72% attained goal BP compared with 59% of the patients younger than 55 years ($p = 0.03$). When the groups were subdivided by race there was still a strong trend indicating a greater percent reaching goal BP with hydrochlorothiazide among the older patients in both racial groups. Unlike the change in average BP the difference in the percent reaching goal BP did not quite reach the 0.05 level of significance. This may have been due to the relatively small sample sizes resulting from both race and age subdivisions. Among whites 65% of those aged 55 to 65 years attained a diastolic BP <90 mm Hg compared with 48% of patients younger than 55 years ($p = 0.08$). As expected, blacks had a greater response rate than whites with 80% responders in the older age group and 67% among the younger patients ($p = 0.12$).

Propranolol: An additional 298 patients were randomly assigned in a double-blind study to propranolol. Of these 107 were aged 55 to 65 years and 191 were below this age. Doses of the drug were titrated from 40 mg twice daily to 320 mg twice daily as needed to achieve goal BP. Reduction of BP averaged -10.6/-11.4 mm Hg in the group aged 55 to 65 years compared with -10.3/-10.5 mm Hg in the patients younger than 55 years (Table I). The differences between these 2 age groups were not significant. There also were no age-related differences when blacks and whites were analyzed separately. However, there were significant age-related differences in response to propranolol when white patients aged ≥60 years were compared with the younger patients. Their systolic BP reduction averaged only -5.4 mm Hg compared with -14.9 mm Hg in patients aged <60 years ($p < 0.001$). The diastolic differences were in the same direction but were not significant. Blacks showed no age-related differences to propranolol in this age group.

Dose requirements: Age-related responsiveness to propranolol and hydrochlorothiazide also was evaluated in terms of the dose of drug required to achieve

TABLE II Percent Attaining Diastolic Blood Pressure <90 mm Hg (Goal Blood Pressure) with Propranolol or Hydrochlorothiazide Above and Below Age 55 Years

	Age <55		Age 55 to 65		p Value
	No.	Attaining Goal BP (%)	No.	Attaining Goal BP (%)	
Hydrochlorothiazide					
Blacks	112	67	59	80	0.12
Whites	79	48	62	65	0.08
All	191	59	121	72	0.03
Propranolol					
Blacks	113	54	57	53	1.00
Whites	78	56	50	70	0.18
All	191	55	107	61	0.40

goal BP. As an index of responsiveness the doses of hydrochlorothiazide were divided into low and high dose ranges; the low dose consisted of 50 or 100 mg and the high dose 200 mg/day. With propranolol the low dose range was 80 to 240 mg and the high dose 320 to 640/day.

In whites only there was a significant difference with age in the percentage of responders to low doses of hydrochlorothiazide. In those aged 55 to 65 years 83% responded to the low doses compared with a 53% response rate to the same dose in those younger than 55 years ($p = 0.01$). There were no significant age-related differences in the dose responsiveness to propranolol.

Medical terminations and age: Medical terminations were not significantly related to age. Terminations were divided into medical and administrative causes. Medical terminations included such events as major cardiovascular complications and elevated BP.

During the 14-week titration period the percent of hydrochlorothiazide-treated patients with medical terminations was 1.0% in patients younger than 55 and 3.0% in those 55 to 65 years of age ($p = 0.16$ by chi-square test), which was an insignificant difference. Medical terminations in the propranolol-treated patients were 4.2% in those younger than 55 years and 6.5% in those 55 to 65 ($p = 0.37$).

Nadolol and Bendroflumethiazide

Another Veterans Administration Cooperative Study⁹ was carried out comparing nadolol (80 to 240 mg/day) with bendroflumethiazide (5 mg increased to 10 mg/day) or the combination of the 2 drugs. The number of randomized patients was 365 and the entry BP was in the range of 95 to 114 mm Hg. The age range was 20 to 69 years (mean 50.5). The average pretreatment diastolic BP in the group younger than 55 years and the group 55 to 69 years was similar. In the patients who received bendroflumethiazide alone the decrease in BP averaged $-20.5/-11.7$ mm Hg in the patients aged 55 to 69 and $-14.8/-11.6$ mm Hg in the group younger than 55. The difference in the systolic reduction between the older and the younger patients was of borderline significance ($p = 0.10$, Student *t* test).

TABLE III Change in Blood Pressure (BP) After Treatment with Hydrochlorothiazide, Captopril or the Combination According to Age

Treatment	Age <55	Age 55 to 69	p Value
Hydrochlorothiazide			
Systolic BP	(n = 28) -12	(n = 43) -10	0.56
Diastolic BP	-7	-9	0.39
Captopril alone*			
Systolic BP	(n = 35) -10	(n = 65) -10	0.89
Diastolic BP	-9	-10	0.73
Captopril plus hydrochlorothiazide			
Systolic BP	(n = 85) -21	(n = 127) -28	0.0015
Diastolic BP	-16	-16	0.69

*Represents one-third of captopril patients who did not have hydrochlorothiazide added.

Nadolol alone resulted in no difference in the degree of BP reduction between the 2 age groups. The average reduction for both groups combined was $-10.6/-12.3$ mm Hg. A significant age-related difference in systolic BP was observed in the patients who received the combination of the diuretic and the β blocker. Patients younger than 55 years showed a systolic reduction of -22.4 while those aged 55 to 69 years averaged -29.2 mm Hg systolic BP reduction ($p = 0.01$). Despite the enhanced response, hypotensive side effects were not reported.

Captopril With and Without a Diuretic

The third study compared the antihypertensive effects of various doses of captopril both alone and with a diuretic¹⁰ in patients with uncomplicated hypertension. The patients were men age 20 to 69 years (mean 55.2) whose diastolic BP during the placebo run-in period was in the range of 92 to 109 mm Hg on 2 successive clinic visits. The regimens were randomly assigned in parallel and double-blind manner. After 7 weeks of captopril alone hydrochlorothiazide, 25 mg twice daily, was added double-blind in two-thirds of the patients.

Of the 421 patients randomly assigned in the trial, 166 were younger than 55 while 255 were aged 55 to 69 years. The average baseline diastolic BP in the 2 age groups <55 and 55 to 69 years was 98.4 and 97.3 mm Hg, respectively. With captopril alone the reductions of BP averaged $-10.3/-10.0$ mm Hg in the group aged 55 to 69 and $-9.8/-9.3$ mm Hg in patients younger than 55 years (Table III). There was no age-related difference in the percent of patients whose diastolic BP decreased to <90 mm Hg compared with those who did not. There were 16% terminations in the group younger than 55 and 11% in those 55 to 69 years.

After the addition of hydrochlorothiazide there was a definite further decrease in BP. The reduction from pretreatment baseline was greater in the group 55 to 69 years of age; it averaged $-27.5/-16.2$ mm Hg compared with $-20.7/-15.7$ mm Hg in the younger group. The systolic difference from baseline was significant ($p < 0.0015$).

A multiple regression analysis of factors predicting changes in diastolic BP with captopril alone indicated that age as a continuous variable contributed very little to the model predicting BP change from baseline to the eighth week of treatment. It accounted for less than 2% of the variability of the BP change. With captopril plus diuretic there was a trend suggesting that the combination was somewhat more effective in older patients.

Discussion

These data demonstrate that age affects the antihypertensive responsiveness to some drugs and not to others. Elderly patients, both black and white, exhibit a significantly greater antihypertensive response to hydrochlorothiazide than younger subjects but this did not occur with β -adrenergic blocking drugs.

The older age group in these studies was between the ages of 55 and either 65 or 69. The very old were excluded. Most patients with isolated systolic hypertension were not included. The group aged 55 to 65 represents an intermediate group between middle-aged and very old patients. They comprise a very large and important proportion of the hypertensive population.² Comparing those older with those younger than 55, the percent of patients receiving hydrochlorothiazide who achieved diastolic BP <90 mm Hg was greater in the older age group. The older white patients also required a lower average dose of hydrochlorothiazide to achieve goal BP. As noted in previous trials there was a significant racial influence: blacks exhibited a greater antihypertensive response to diuretics than did whites.^{8,9,11}

There were no age-related differences with propranolol (Table I). Most other studies agree with the present results, that there is no correlation between age and the response to β -adrenergic blocking drugs.¹²⁻¹⁴ However, when we compared only white patients aged 60 to 65 with the patients younger than 60 years there was a significant blunting of the antihypertensive response to propranolol among the older patients. This diminished response in patients aged 60 to 65 years confirms the observations of Buhler et al,¹⁵ who found that only 20% of these patients achieved a diastolic BP <90 mm Hg compared with 50% of patients 40 to 60 years of age.

The diuretic bendroflumethiazide, administered alone, was also more effective in patients aged 55 to 69 years compared with those younger than 55 years, although the difference reached only borderline ($p = 0.10$) significance. Also, the combination of diuretic plus β blockade resulted in a significantly greater decrease in systolic BP in the older patients compared with the younger group ($p = 0.01$). Nadolol alone failed to show a significant difference in BP related to age.

An age-related effect of diuretics also was found in the third study involving captopril and hydrochlorothiazide. When captopril alone was administered there was no significant age-related difference in BP. When hydrochlorothiazide was added, the response was significantly greater in the older age group. There-

fore, in all 3 trials the antihypertensive effectiveness of the diuretic was greater in the older patients.

The Hypertension Detection and Follow-up Program,¹¹ which prescribed diuretics as primary treatment also found an enhanced antihypertensive response in the older age groups compared with younger patients. Not only was the average BP lower but there also was a greater reduction in mortality in the step care compared with the referred care patients in the older age groups.

The European Working Party on High Blood Pressure in the Elderly¹⁶ found a significant decrease in BP in patients older than 60, which averaged $-20/-8$ mm Hg lower than the placebo control subjects. These patients were treated with 25 mg hydrochlorothiazide plus 50 mg triamterene daily, with α methyldopa added when needed. Side effects in some patients consisted of increases in creatinine and uric acid, but not in cholesterol, and impairment of glucose tolerance after 2 years of treatment. In general, however, the medications were well tolerated.

In the present studies drug-related symptoms including mental symptoms were not significantly greater in the group aged 55 to 65 years than in the younger patients. Lindeman et al¹⁷ administered hydrochlorothiazide-reserpine treatment to elderly patients in a placebo-controlled double-blind trial. They failed to find any changes in psychological tests or in the electroencephalogram before and after treatment despite considerable decreases in BP in some patients. In 14 patients the reductions in BP were considerable, averaging -51 mm Hg systolic and -21 mm Hg diastolic.

Elderly patients may develop hypotensive reactions when treated with certain antihypertensive agents. For example, among the drugs used in 1955, Freis¹⁸ found that reserpine, veratrum and hydralazine were better tolerated than pentolinium, a ganglion blocking drug. The latter resulted in more hypotensive symptoms, particularly postural hypotension in the elderly. Jackson et al¹⁹ warned of the dangers of treating elderly patients. They reported 6 patients aged 64 to 84 who were usually treated with a thiazide plus methyldopa. The side effects consisted mostly of hypotensive symptoms.

Many of these side effects, including hypotensive side effects in the elderly, can be avoided by initiating treatment with half doses of antihypertensive drugs. These doses are then increased gradually as needed until the desired response occurs. Antihypertensive reactions were not seen in the present trials nor were they observed in the Australian trial on the treatment of mild hypertension in the elderly.⁶ The latter study used 300 to 1,000 mg/day of chlorothiazide as initial therapy followed by step 2 drugs as needed.

Hemodynamic changes that may affect the antihypertensive responses with aging include reductions in cardiac output, heart rate, stroke volume, intravascular volume, renal blood flow and plasma renin activity.¹ Plasma volume appears to correlate inversely with total peripheral resistance, which is increased. Because plasma volume is already somewhat reduced in the

elderly, the further reduction induced by thiazides may contribute to the enhanced antihypertensive response found in the elderly. For any given level of BP elderly hypertensive patients exhibit more hypertrophy of the left ventricle than do younger patients. Renal blood flow is reduced. One of the most important changes with aging with respect to cardiovascular control is the alteration in the baroreceptors.²⁰ With increasing age and associated increased stiffness of the carotid arteries the baroreceptors become less effective in modifying BP changes including the reductions induced by antihypertensive drugs including orthostatic hypotension.

It can be concluded that antihypertensive drug therapy is effective and well tolerated in elderly patients with uncomplicated hypertension. However, reasonable precautions should be taken when prescribing thiazide diuretics in the elderly because of the increased antihypertensive responsiveness of such patients to these agents. In elderly patients diuretic treatment should probably begin with half doses and then increased as needed. Additional studies are needed to determine if elderly patients with cardiovascular complications, such as old myocardial infarction, stroke or congestive heart failure, can tolerate drug treatment as well as the present patients who had no complications. Also needed are studies of responses to antihypertensive drugs in patients older than 65 or 69 years and especially in those with isolated systolic hypertension.

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